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Published in:
International Journal of Drug Policy

DOI:
[10.1016/j.drugpo.2019.01.011](https://doi.org/10.1016/j.drugpo.2019.01.011)

Publication date:
2019

Licence:
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Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Grebely, J., Dore, G. J., Alami, N. N., Conway, B., Dillon, J. F., Gschwantler, M., Felizarta, F., Hézode, C., Tomasiewicz, K., Fredrick, L. M., Dumas, E. O., & Mensa, F. J. (2019). Safety and efficacy of glecaprevir/pibrentasvir in patients with chronic hepatitis C genotypes 1-6 receiving opioid substitution therapy. *International Journal of Drug Policy*, 66, 73-79. <https://doi.org/10.1016/j.drugpo.2019.01.011>

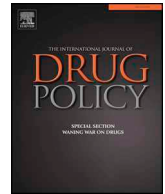
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Research Paper

Safety and efficacy of glecaprevir/pibrentasvir in patients with chronic hepatitis C genotypes 1–6 receiving opioid substitution therapy



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ARTICLE INFO

Keywords:

Glecaprevir/pibrentasvir
Hepatitis C virus
Opioid substitution therapy
People who inject drugs

ABSTRACT

Background: International guidelines recommend treatment of hepatitis C virus (HCV) infection in people who inject drugs (PWID), including those on opioid substitution therapy (OST). The pangenotypic combination of glecaprevir and pibrentasvir has shown high sustained virologic response at post-treatment Week 12 (SVR12) in clinical trials. Herein, we evaluate the safety and efficacy of glecaprevir/pibrentasvir in patients receiving OST. **Methods:** Pooled data from patients with HCV genotypes 1–6 who were treated with glecaprevir/pibrentasvir for 8, 12, or 16 weeks in eight Phase 2 and 3 trials were categorized by use of OST. Treatment completion, treatment adherence, SVR12, adverse events (AEs), and laboratory abnormalities were evaluated for patients receiving and not receiving OST.

Results: Among 2256 patients, 157 (7%) were receiving OST. Compared with patients not receiving OST, OST patients were younger (mean age, 46.8 vs 52.8 years), male (69% vs 54%), white (93% vs 80%), HCV treatment-naïve (86% vs 72%), had HCV genotype 3 (60% vs 26%), and had a history of depression or bipolar disorder (43% vs 19%). Most patients completed (OST: 98% [n/N = 154/157]; non-OST: 99% [n/N = 2070/2099]) and were adherent (received ≥ 90% of study drug doses) to glecaprevir/pibrentasvir treatment (OST: 98% [n/N = 121/123]; non-OST: 99% [n/N = 1884/1905] among patients with available data). In the intention-to-treat population, SVR12 rates in OST and non-OST patients were 96.2% (n/N = 151/157; 95% CI 93.2–99.2) and 97.9% (n/N = 2055/2099; 95% CI 97.3–98.5), respectively. For OST patients, reasons for nonresponse included virologic relapse (< 1%; n = 1), premature study drug discontinuation (< 1%; n = 1), and loss to follow-up (3%; n = 4). AEs occurring in ≥ 10% of OST patients were headache, fatigue, and nausea. Drug-related serious AEs, AEs leading to study drug discontinuation, and Grade 3 or higher laboratory abnormalities were infrequent in both groups (< 1%). No HCV reinfections occurred through post-treatment Week 12.

Conclusion: Glecaprevir/pibrentasvir is highly efficacious and well tolerated in HCV-infected patients receiving OST.

Introduction

The World Health Organization (WHO) recommends that all individuals with chronic hepatitis C virus (HCV) infection should be

assessed for antiviral treatment, and that people who inject drugs (PWID) should be prioritized for treatment given the increased risk of HCV-related disease and HCV transmission in this population (WHO, 2016). In many countries, injection drug use is the primary mode of

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<https://doi.org/10.1016/j.drugpo.2019.01.011>

transmission for HCV (Hajarizadeh, Grebely, & Dore, 2013). In PWID, the prevalence of HCV is estimated to be more than 50% (Degenhardt et al., 2017), including persons receiving opioid substitution therapy (OST) for the management of opioid use disorder.

Despite the rising burden of HCV infection in PWID (Hajarizadeh et al., 2013) and current international guidelines supporting HCV treatment for this group (AASLD/IDSA, 2018; EASL, 2018; Grebely et al., 2015; WHO, 2016), treatment uptake in PWID remains sub-optimal. This is in part because of physicians' concerns about poor treatment adherence and outcomes, or the risk of HCV reinfection (Alavi et al., 2013; Asher et al., 2016; Gidding et al., 2011; Harris & Rhodes, 2013; Wolfe et al., 2015). In addition, payers in the United States and Europe have implemented restrictions that exclude individuals who have recently used illicit drugs from receiving HCV therapies, irrespective of disease stage (Barua et al., 2015; Marshall et al., 2018; Ooka, Connolly, & Lim, 2017).

The availability of newer direct-acting antiviral (DAA) therapies for the treatment of chronic HCV infection, which have shorter and more convenient regimens than previous interferon-based treatments, may increase treatment access in PWID and people receiving OST, thereby reducing the global HCV burden. Evidence from Phase 3 trials suggests that combinations of all-oral, interferon-free DAA drugs have high efficacy and are well tolerated in patients receiving OST (Dore et al., 2016; Grebely et al., 2016; Hajarizadeh et al., 2018). However, the majority of studies performed to date enrolled small numbers of patients with HCV genotypes 2–6, and excluded patients with ongoing drug use.

The DAA combination of glecaprevir/pibrentasvir has recently been approved for the treatment of HCV genotypes 1–6 (Mavyret, 2017). In Phase 2 and 3 trials, the once-daily, all-oral, ribavirin-free combination of glecaprevir/pibrentasvir for 8, 12, or 16 weeks was well tolerated and demonstrated high sustained virologic response at post-treatment Week 12 (SVR12) across HCV genotypes 1–6, with SVR12 rates of 99% in patients with genotype 1 and 95–98% in patients with genotype 3 (Gane et al., 2017; Asselah et al., 2017; Forns et al., 2017; Gane et al., 2016; Mavyret, 2017; Zeuzem et al., 2018). In a Phase 1 study in HCV-negative individuals receiving OST, no clinically relevant drug–drug interactions were observed when glecaprevir/pibrentasvir was coadministered with methadone or buprenorphine-naloxone therapy (Kosloski et al., 2017). However, there are no published Phase 3 studies on the efficacy and safety of glecaprevir/pibrentasvir in HCV-infected patients receiving OST.

The aim of this post hoc analysis was to evaluate treatment completion, treatment adherence, efficacy, and safety of glecaprevir/pibrentasvir in patients infected with HCV genotypes 1–6 receiving OST, including those patients with recent illicit drug use, compared with those not receiving OST.

Methods

Study patients and design

Data were pooled from eight international Phase 2 and 3 trials of glecaprevir/pibrentasvir: SURVEYOR-1 and -2 (ClinicalTrials.gov identifiers: NCT02243280 and NCT02243293) (Asselah et al., 2017; Gane et al., 2016), ENDURANCE-1, -2, -3, and -4 (NCT02604017, NCT02640482, NCT02640157, and NCT02636595) (Asselah et al., 2017; Zeuzem et al., 2018), and EXPEDITION-1 and -4 (NCT02642432 and NCT02651194) (Forns et al., 2017; Gane et al., 2017).

Patients 18 years of age or older and chronically infected with HCV genotypes 1–6, with compensated cirrhosis or without cirrhosis, were enrolled in the trials. Cirrhosis assessment was based on liver biopsy, FibroScan® (Echosens, Waltham, MA, USA), or a combination of FibroTest™ (BioPredictive, Paris, France) and aspartate aminotransferase-to-platelet ratio index. Patients were either HCV treatment-naïve or -experienced with interferon or pegylated interferon ± ribavirin,

or sofosbuvir + ribavirin ± pegylated interferon. Patients coinfecting with more than one HCV genotype and patients coinfecting with hepatitis B virus (HBV) were excluded from the trials.

Patients reporting stable OST use (defined as OST use for at least 6 months prior to screening) were eligible to enroll in all trials included in this analysis. ENDURANCE-1, -2, -3, and -4 and EXPEDITION-1 and -4 (Phase 3 trials) included patients with illicit drug use, unless they had a recent (within 6 months prior to study drug administration) history of drug or alcohol use that could preclude adherence to the protocol in the opinion of the investigator. SURVEYOR-1 and -2 (Phase 2 trials) excluded patients with illicit drug use detected by a positive urine drug test at screening.

In patients receiving OST enrolled in the Phase 3 trials, we identified persons who use drugs (PWUD) who self-reported injection drug use within 12 months prior to screening and/or had illicit drug use detected by a positive urine drug test at screening (defined as recent PWUD). Illicit drugs detected by a positive urine drug test included cocaine, amphetamines, phencyclidine, propoxyphene, heroin, or other opioids that could not be accounted for by concomitant prescribed medications taken for medical diagnoses (eg, prescribed methadone or buprenorphine for opioid use disorder). Patients in the Phase 3 trials who had treatment-emergent adverse events (AEs) consistent with use of the aforementioned drugs (identified by the Drug Abuse, Dependence and Withdrawal Standardized MedDRA® Queries [International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland]) were also considered to be recent PWUD.

Patients received glecaprevir 300 mg/pibrentasvir 120 mg once daily for 8, 12, or 16 weeks. Study designs and patient eligibility criteria have been previously described in detail (Asselah et al., 2017; Forns et al., 2017; Gane et al., 2016, 2017; Zeuzem et al., 2018).

Study endpoints

The following endpoints were assessed in this analysis: treatment completion, treatment adherence, SVR12, and safety. Patients were considered to have completed treatment if they did not discontinue study drug prior to their scheduled final treatment period visit at Week 8, 12, or 16 for those assigned to 8, 12, or 16 weeks of treatment, respectively. Patients were considered to be adherent to treatment if they received at least 90% of study drug doses; the percentage of study drug doses received was calculated by dividing the total number of pills received during therapy (determined by pill counts during study visits at Weeks 8, 12, and 16 [where applicable]) by the total expected number of pills. Patients with missing adherence data because of incomplete pill count records were excluded from adherence analyses. SVR12 was defined as an HCV RNA concentration below the lower limit of quantification (LLOQ) at post-treatment Week 12, measured using the COBAS® TaqMan® HCV Test, v2.0 (LLOQ 15 IU/mL; Roche Molecular Systems, Basel, Switzerland) or the COBAS® TaqMan® Real-time Reverse Transcription-PCR Assay, v2.0 (LLOQ 25 IU/mL; Roche Molecular Systems, Basel, Switzerland). Virologic failure was defined as on-treatment virologic failure (breakthrough or end-of-treatment [EOT] failure) or post-treatment virologic relapse. Patients were monitored for HCV reinfection during the 12 weeks following EOT. Phylogenetic analyses were used to distinguish reinfection from virologic failure. Safety was assessed using treatment-emergent AEs and clinical laboratory abnormalities. AEs were recorded using MedDRA version 19.

Statistical analysis

The analysis population included all patients who received at least 1 dose of glecaprevir/pibrentasvir (intention-to-treat [ITT] analysis). Descriptive statistics including means, standard deviations, frequencies, and percentages were used to summarize the data. Baseline demographics and clinical characteristics of patients receiving OST and those not receiving OST were compared using chi-square tests (categorical data)

and one-way analysis of variance (continuous data). The percentages of patients with treatment completion, treatment adherence, SVR12, AEs, and post-baseline Grade ≥ 3 clinical laboratory abnormalities (with grade worse than baseline grade) were calculated for patients receiving OST and those not receiving OST. Two-sided 95% confidence intervals (CIs) for SVR12 rates were calculated using the normal approximation to the binomial distribution. Patients with missing SVR12 data were counted as virologic failures unless the nearest HCV RNA value after the SVR12 visit window was below the LLOQ, in which case they were counted as achieving SVR12. A modified ITT (mITT) analysis was performed for SVR12, which excluded patients with nonvirologic failure. Statistical analyses were conducted using SAS[®] software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Of the 2256 patients across the eight clinical trials included in the ITT population, 157 patients (7%) were receiving OST at baseline (of which 39 patients were in Phase 2 trials and 118 patients were in Phase 3 trials). The demographics and clinical characteristics at baseline are shown in Table 1. Compared with patients not receiving OST, those receiving OST were younger (mean age, 46.8 vs 52.8 years), male (69% vs 54%), white (93% vs 80%), and HCV treatment-naïve (86% vs 72%). More patients receiving OST had HCV genotype 3 (60% vs 26%) and a history of depression or bipolar disorder (43% vs 19%) compared with those not receiving OST. Fewer patients receiving OST had a history of cardiovascular disease (24% vs 33%) compared with those not receiving OST. Three patients receiving OST had HIV coinfection (all were enrolled in ENDURANCE-1). Methadone was the most commonly prescribed OST (76%). Of 118 patients receiving OST in Phase 3 trials (excluding Phase 2 trials for which a positive urine drug screen result at screening was exclusionary), 26 patients (22%) were recent PWUD. Of these 26 patients, 10 patients (38%) self-reported injection drug use within 12 months prior to screening, 14 patients (54%) had a positive urine drug test at screening, and 2 patients (8%) self-reported injection drug use within 12 months prior to screening and had a positive urine drug test at screening.

Treatment completion and adherence

The percentage of patients who completed therapy with glecaprevir/pibrentasvir was 98% (n/N = 154/157) in patients receiving OST and 99% (n/N = 2070/2099) in those not receiving OST (Table 2). Three patients (2%) receiving OST discontinued therapy: 1 patient was non-adherent to the study drugs and 2 patients discontinued for other reasons (1 patient was found to be pregnant; 1 patient self-discontinued study drug). Twenty-nine patients (1%) not receiving OST discontinued therapy, in whom the primary reasons for discontinuation were as follows: 11 patients had AEs; 6 patients were non-adherent to the study drugs; 3 patients had virologic failure; 3 patients withdrew consent; 3 patients were lost to follow-up; 3 patients discontinued for other reasons (1 patient was found to be pregnant; 2 patients self-discontinued study drug). The percentage of patients who were adherent to treatment (ie, received $\geq 90\%$ of study drug doses) was 98% (n/N = 121/123) in patients receiving OST and 99% (n/N = 1884/1905) in those not receiving OST among patients with available data (Table 2).

Efficacy

In the ITT analysis, the SVR12 rate in the overall population was 97.8% (n/N = 2206/2256; 95% CI 97.2–98.4). The SVR12 rates in patients receiving and not receiving OST were 96.2% (n/N = 151/157; 95% CI 93.2–99.2) and 97.9% (n/N = 2055/2099; 95% CI 97.3–98.5),

Table 1
Baseline demographics and clinical characteristics.

Baseline characteristic	Receiving OST (N = 157)	Not receiving OST (N = 2099)
Male, n (%) ^a	109 (69)	1127 (54)
Race, n (%) ^{a,b}		
White	146 (93)	1671 (80)
Black or African American	3 (2)	116 (6)
Asian	4 (3)	266 (13)
Other	4 (3)	43 (2)
Age [years], mean (SD) ^a	46.8 (10.36)	52.8 (11.98)
BMI [kg/m ²], mean (SD)	27.0 (5.90)	26.5 (5.00)
HCV RNA [log ₁₀ IU/mL], mean (SD)	6.1 (0.83)	6.1 (0.78)
History of cardiovascular disease, n (%) ^a	37 (24)	692 (33)
History of depression or bipolar disorder, n (%) ^a	67 (43)	409 (19)
Current tobacco use, n (%) ^{a,c}	113 (72)	725 (35)
Current alcohol use, n (%) ^d	44 (28)	699 (33)
Recent PWUD, n/N (%)	26/118 (22)	n/a
HCV genotype, n (%) ^a		
1	41 (26)	848 (40)
2	17 (11)	449 (21)
3	94 (60)	549 (26)
4–6	5 (3)	253 (12)
Fibrosis stage, n (%) ^e		
F0–F1	104 (66)	1487 (71)
F2	11 (7)	144 (7)
F3	14 (9)	214 (10)
F4	28 (18)	249 (12)
HCV treatment-naïve, n (%) ^a	135 (86)	1505 (72)
Type of OST, n (%) ^f		
Methadone	119 (76)	–
Buprenorphine	19 (12)	–
Morphine sulfate	5 (3)	–
Not reported	14 (9)	–

BMI, body mass index; HCV, hepatitis C virus; n/a, not available; OST, opioid substitution therapy; PWUD, people who use drugs; RNA, ribonucleic acid; SD, standard deviation.

^a Statistically significant ($p < 0.05$) difference between groups based on chi-square test for categorical data and one-way analysis of variance for continuous data.

^b Race was missing for 3 patients (0.1%) who were not receiving OST.

^c Tobacco use status was unknown for 5 patients (0.2%) who were not receiving OST.

^d Alcohol use status was unknown for 9 patients (0.4%) who were not receiving OST.

^e Fibrosis stage was missing for 5 patients (0.2%) who were not receiving OST.

^f Patients who reported being on stable OST but did not report a specific therapy (ie, methadone, buprenorphine, or morphine sulfate) were listed under “Not reported”.

respectively (Fig. 1). SVR12 rates across HCV genotypes were comparable between patients receiving and not receiving OST (Fig. 2). In patients infected with HCV genotype 3, SVR12 rates were 95% in both groups. In patients who were not adherent to treatment (ie, received $< 90\%$ of study drug doses), the overall SVR12 rate was 90.9% (n/N = 20/22; 95% CI 78.9–100). All three patients receiving OST with HIV coinfection achieved SVR12. In the mITT analysis, which excluded patients who failed to achieve SVR12 for nonvirologic reasons, SVR12 rates were 99.3% (n/N = 151/152; 95% CI 98.1–100) in patients receiving OST and 98.9% (n/N = 2055/2077; 95% CI 98.5–99.4) in those not receiving OST.

The reasons for non-SVR12 in patients receiving and not receiving OST are shown in Fig. 1. In patients receiving OST, there was 1 virologic relapse and 1 premature discontinuation of treatment (both patients had genotype 3 infection); 4 patients (3%) were lost to follow-up (3 patients had genotype 3 infection), defined as missing SVR12 data between EOT and post-treatment Week 12. The patient with virologic

Table 2
Treatment completion and adherence.

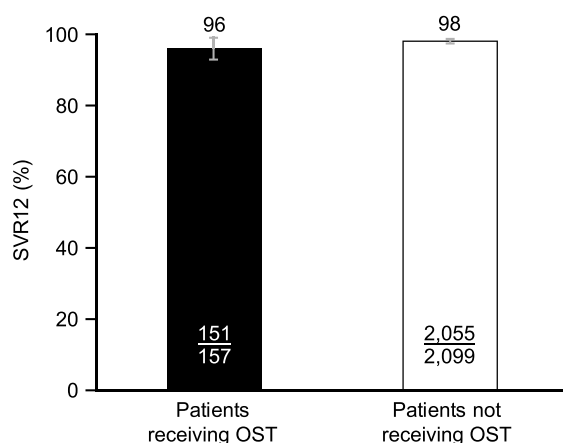
	Receiving OST (N = 157)	Not receiving OST (N = 2099)
Treatment completion, n/N (%)	154/157 (98)	2070/2099 (99)
Treatment adherence, ^a n/N ^b (%)	121/123 (98)	1884/1905 (99)

OST, opioid substitution therapy.

N = total number of patients in each subgroup; n = number of patients with treatment completion or treatment adherence.

^a Treatment adherence was considered $\geq 90\%$ of study drug doses based on pill counts.

^b Patients with missing drug accountability records were not assessed for adherence (therefore, total adherence N is lower than total patients enrolled).



Virologic failure	1 (<1%) ^a	22 (1%) ^b
Premature D/C	1 (<1%)	11 (<1%)
Lost to follow-up	4 (3%)	11 (<1%)
HCV reinfection	0	0

Fig. 1. Overall SVR12 by intention-to-treat analysis.

Error bars represent 95% confidence intervals.

D/C, discontinuation; HCV, hepatitis C virus; OST, opioid substitution therapy; SVR12, sustained virologic response at post-treatment Week 12.

^a 1 patient had post-treatment virologic relapse.

^b 5 patients had on-treatment virologic breakthrough; 17 patients had post-treatment virologic relapse.

relapse was a 49-year-old white male with no baseline polymorphisms in either NS3 or NS5A. The patient was adherent to study drug and had normal glecaprevir and pibrentasvir drug exposures. The patient who discontinued treatment prematurely did so on Day 62 because of non-adherence to the study drug. Both patients were non-cirrhotic, HCV treatment-naïve, receiving methadone, and assigned to treatment for 12 weeks with glecaprevir/pibrentasvir in the ENDURANCE-3 study (Zeuzem et al., 2018). In patients not receiving OST, 22 patients had virologic failure (5 patients [$< 1\%$] had on-treatment virologic breakthrough; 17 patients [$< 1\%$] had virologic relapse), 11 patients ($< 1\%$) discontinued treatment prematurely, and 11 patients ($< 1\%$) were lost to follow-up. There were no reported cases of HCV reinfection.

Of the 26 patients receiving OST who were recent PWUD, 22 patients achieved SVR12 (84.6%; n/N = 22/26). Reasons for not achieving SVR12 were as follows: 1 patient discontinued because of non-compliance; 1 patient had virologic relapse; 1 patient had EOT virologic response, but did not follow-up in the post-treatment period; and 1 patient did not follow-up for SVR12, but had EOT virologic response and SVR24. Of the 92 patients receiving OST who were not recent PWUD, 90 patients achieved SVR12 (97.8%; n/N = 90/92). Reasons for not achieving SVR12 were as follows: 1 patient had missing SVR12 and 1 patient was lost to follow-up.

Safety

Overall, 117 patients (75%) receiving OST and 1403 patients (67%) not receiving OST experienced at least 1 AE (Table 3). Headache, fatigue, and nausea were the most common AEs experienced by patients in either group. Seventy-five patients (48%) receiving OST and 844 patients (40%) not receiving OST had AEs that were considered by the investigator to be possibly related to the study drugs. Eight patients (5%) receiving OST and 62 patients (3%) not receiving OST had a serious AE. No DAA-related serious AEs or AEs leading to discontinuation of the

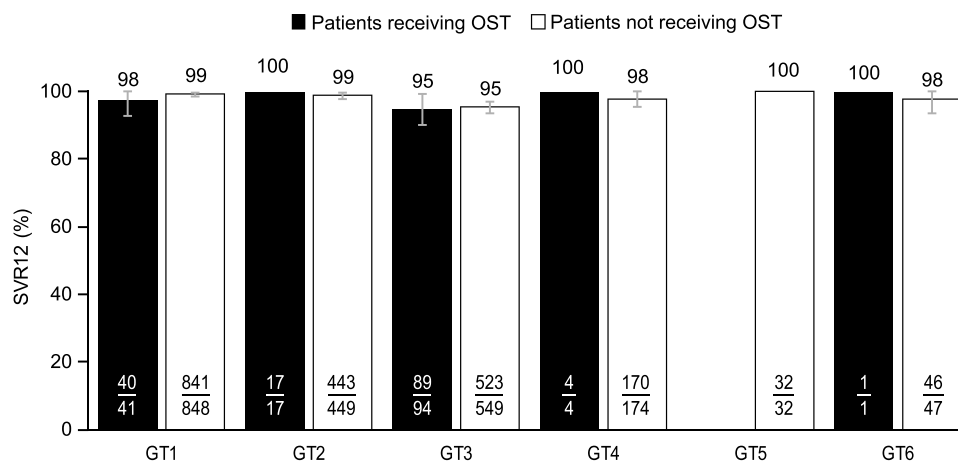


Fig. 2. SVR12 rates across HCV genotypes by intention-to-treat analysis.

Error bars represent 95% confidence intervals.

GT, genotype; HCV, hepatitis C virus; OST, opioid substitution therapy; SVR12, sustained virologic response at post-treatment Week 12.

Table 3
Summary of adverse events.

Adverse event, n (%)	Receiving OST (N = 157)	Not receiving OST (N = 2099)
Any AE	117 (75)	1403 (67)
Any DAA-related ^a AE	75 (48)	844 (40)
Serious AE	8 (5)	62 (3)
DAA-related ^a serious AE	0	1 (< 1) ^b
AE leading to study drug discontinuation	0	12 (< 1)
DAA-related ^a AE leading to study drug discontinuation	0	5 (< 1) ^c
AEs occurring in ≥10% of patients		
Headache	32 (20)	362 (17)
Fatigue	28 (18)	305 (15)
Nausea	21 (13)	189 (9)
Death ^d	1 (< 1)	5 (< 1)

AE, adverse event; DAA, direct-acting antiviral; OST, opioid substitution therapy.

^a Relatedness of AEs to DAAs was determined by the investigator.

^b Transient ischemic attack judged to be DAA-related by the investigator; the patient discontinued treatment on Day 12 and did not achieve SVR12. The patient had multiple cardiovascular risk factors at baseline.

^c Diarrhea; abdominal pain; dizziness; dyspepsia; fatigue; headache; malaise; nausea; pruritus; transient ischemic attack.

^d All deaths occurred in the post-treatment period and all were considered unrelated to the study drugs by the investigator. Patient receiving OST: alcohol poisoning and toxicity to various drugs (per the autopsy, it was thought to be a lethal combination of alcohol and methadone). Patients not receiving OST: pneumonia; accidental overdose; cerebral hemorrhage; adenocarcinoma; cerebral hemorrhage.

Table 4
Laboratory abnormalities.

Event, n (%) ^a	Receiving OST (N = 157)	Not receiving OST (N = 2097)
Alanine aminotransferase		
Grade ≥3 (> 5 × ULN)	0	2 (< 1)
Aspartate aminotransferase		
Grade ≥3 (> 5 × ULN)	1 (< 1)	5 (< 1)
Total bilirubin		
Grade ≥3 (> 3 × ULN)	0	9 (< 1)
Hemoglobin		
Grade ≥3 (< 8 g/dL)	1 (< 1)	6 (< 1)

N = total number of patients with observed laboratory values.

OST, opioid substitution therapy; ULN, upper limit of normal.

^a Post-baseline grade must have been more extreme than baseline grade.

study drugs occurred in patients receiving OST; the incidence of these events in patients not receiving OST was low (< 1%).

Post-baseline laboratory abnormalities were infrequent in patients receiving OST (Table 4). One patient each (< 1%) had a Grade ≥3 elevation in aspartate aminotransferase concentration and a Grade ≥3 decrease in hemoglobin concentration. Among patients who were not receiving OST, 2 patients (< 1%) had a Grade ≥3 elevation in alanine aminotransferase (ALT) concentration. One patient had a Grade 2 elevation in ALT concentration at baseline (215 U/L), followed by a Grade 3 elevation (278 U/L) at Week 1. The concentration decreased to 131 U/L thereafter, and normalized with continued treatment. The other patient had an ALT elevation in the context of multiple gallstones.

Nine patients (< 1%) not receiving OST had Grade ≥3 elevations in total bilirubin concentrations. These patients had indirect predominance, and all of them had elevated bilirubin concentrations at baseline; there were no associated post-baseline ALT elevations by grade.

Discussion

In this post hoc analysis of pooled data from eight Phase 2 and 3 trials of patients chronically infected with HCV genotypes 1–6, including a large population of patients with HCV genotype 3, once-daily glecaprevir/pibrentasvir for 8, 12, or 16 weeks demonstrated high efficacy across HCV genotypes regardless of OST with no observed HCV reinfections and low rates of premature discontinuation. Treatment was well tolerated, with a safety profile that was comparable between patients receiving OST and those not receiving OST. This study provides additional data to support the initiation of DAA treatment in people receiving OST, consistent with international guidelines (AASLD/IDSA, 2018; EASL, 2018; Grebely et al., 2015; WHO, 2016). Furthermore, this study provides data on the safety and efficacy of DAAs in patients with HCV genotype 3 who are receiving OST, addressing a gap in other post hoc analyses of Phase 3 trials (Dore et al., 2016; Grebely et al., 2016; Grebely, Puoti et al., 2018; Hajarizadeh et al., 2018). This is particularly important given the high prevalence of HCV genotype 3 among PWID globally (Robaey, Bielen, Azar, Razavi, & Nevens, 2016).

The availability of well tolerated and efficacious all-oral DAA regimens with short treatment durations is important for upscaling HCV treatment and eradicating HCV infection in PWUD. Glecaprevir/pibrentasvir is a pangenotypic DAA regimen indicated for 8 weeks in HCV treatment-naïve patients without cirrhosis (Mavyret, 2017), who comprise the majority of the HCV-infected population in the real world (Chirikov, Marx, Manthena, Strezewski, & Saab, 2018), and therefore meets this unmet need. However, upscaling treatment will remain problematic in PWUD because of barriers such as limited access to care. Patients on stable OST represent a discrete group for whom priority treatment can be considered amenable because they are generally more closely linked to care than current or recent PWID. Studies have shown that integrating DAA therapy into existing drug treatment programs improves the rate of successful HCV treatment in the OST population (Butner et al., 2017; Dore et al., 2016; Lalezari et al., 2015).

Treatment completion and adherence with glecaprevir/pibrentasvir were similarly high for patients receiving OST and those not receiving OST, which is consistent with reports from post hoc analyses of patients receiving OST in Phase 3 clinical trials of sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, or ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (Dore et al., 2016; Grebely et al., 2016; Grebely, Puoti et al., 2018; Hajarizadeh et al., 2018). Furthermore, adherence was high in the OST group despite the inclusion of patients who were classified as recent PWUD (22% of patients receiving OST in Phase 3 trials). In a Phase 3 trial of elbasvir/grazoprevir for 12 weeks in patients receiving OST (including patients with ongoing drug use), adherence > 95% was reported by > 95% of patients and 99% completed DAA therapy, although those patients had the added benefit of a daily adherence reminder (Dore et al., 2016).

Our findings show that virologic failure with glecaprevir/pibrentasvir was low regardless of OST use. The main reason for not achieving SVR12 in patients receiving OST was loss to follow-up between EOT and post-treatment Week 12. The individuals who were lost to follow-up completed treatment and attained an EOT response, so it is likely they would have achieved SVR12. The proportion of patients with missing SVR12 data because of loss to follow-up was low in patients receiving OST and those not receiving OST (3% [4/157] and < 1% [11/2099], respectively). The issue of loss to follow-up has been observed in real-world studies in people with a history of injection drug use treated with DAA therapies (Christensen et al., 2018; Hajarizadeh et al., 2018; Mason et al., 2017; Morris et al., 2017; Read et al., 2017). However, loss to follow-up was reduced when OST and HCV services were colocated in the same medical institution, highlighting the importance of integrating HCV care in drug treatment settings (Christensen et al., 2018).

Physicians often cite concerns about the rate of HCV reinfection as a reason for reluctance to give DAA therapy to HCV-infected PWID (Asher et al., 2016). No reinfections were observed in this study, although follow-up was limited to 12 weeks after EOT in all trials included in the analysis. In previous studies in people with a history of injection drug use or in people receiving OST, reinfection rates have ranged from 1 to 5% per 100 person-years following successful interferon-based therapy (Aspinall et al., 2013; Cunningham, Applegate, Lloyd, Dore, & Grebely, 2015; Midgard et al., 2016; Simmons, Saleem, Hill, Riley, & Cooke, 2016) or DAA-based therapy (Dore et al., 2016; Grebely, Dalgard et al., 2018) with higher rates of reinfection reported in those patients with ongoing injection drug use following treatment. As such, strategies to minimize the risk of reinfection in high-risk groups need to be intensified in parallel with scale-up of DAA therapy in order to prevent HCV transmission.

This study has several limitations. First, this is a post hoc analysis of Phase 2 and 3 clinical trials and the results should be considered for the purposes of hypothesis generation only. Second, individuals who reported drug or alcohol use within 6 months prior to study drug administration were excluded from the trials if deemed unable to adhere to the study protocol in the opinion of the investigator. Also, the proportion of patients who injected or used drugs during the trials is unknown. As such, these findings cannot be generalized to current PWUD who may or may not be receiving OST. Third, there was no long-term follow-up of patients on OST to assess late virologic relapse or HCV reinfection after achieving SVR12. Real-world studies are needed to assess outcomes after DAA treatment in PWID and people on OST, and identify factors associated with reinfection, to provide data on the cost-effectiveness of therapy in this high-risk population (Grebely et al., 2017). A strength of this analysis was the inclusion of Phase 3 studies that allowed patients with recent drug use to enroll, which included people who used injection drugs within 12 months of screening or had a positive urine drug test at screening. Therefore, this study population is less selective than other clinical studies, which often excluded recent PWUD, and is potentially more representative of the broader OST population.

Glecaprevir/pibrentasvir is a well-tolerated and efficacious pan-genotypic treatment option for chronic HCV-infected patients receiving OST, with high rates of treatment completion and adherence achieved in this population. These data add to the body of evidence supporting the use of DAAs in people receiving OST, a high-priority population with a significant burden of chronic HCV infection. Large clinical trials are in progress to evaluate other DAAs in current or former PWID with HCV infection (NCT02498015; NCT02940691; NCT02625909).

Funding

AbbVie sponsored the study; contributed to its design; and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the publication.

Declarations of interest

The design, study conduct, analysis, and financial support of the SURVEYOR-1 and -2, ENDURANCE-1, -2, -3 and -4, and EXPEDITION-1 and -4 studies were sponsored by AbbVie.

J Grebely: Advisor/Research Support: AbbVie, Bristol-Myers Squibb, Cepheid, Gilead Sciences, Merck, MSD. **GJ Dore:** Consultant/Advisor/Research Support: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck. **B Conway:** Research Support/Advisor: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck. **JF Dillon:** Research Support/Speaker: Gilead, Merck, Janssen, Roche, AbbVie. **M Gschwantler:** Advisor/Speaker: Janssen, MSD, Bristol-Myers Squibb, Gilead, AbbVie; Research Support: Gilead, AbbVie, MSD. **F Felizarta:** Research Support: AbbVie, Janssen, Merck; Speaker: AbbVie, Gilead, Merck. **C Hézode:** Personal fees: AbbVie, Bristol-Myers Squibb, Gilead,

Janssen, Merck. **K Tomasiewicz:** Consultancy/Advisory Board/Speaker: AbbVie, Alfa Wasserman, Bristol-Myers Squibb, Gilead, Janssen, MSD, Roche; Grant/Research: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, MSD, Roche. **NN Alami, LM Fredrick, EO Dumas, and FJ Mensa:** Employees of AbbVie; may hold AbbVie stock or options.

All authors had access to relevant data, and participated in the writing, review, and approval of the final manuscript.

Acknowledgments

Glecaprevir was identified by AbbVie and Enanta. The authors would like to express their gratitude to the patients who participated in these studies, and their families, as well as the investigators and coordinators of the studies. The authors would also like to thank Wenjing Lu, of AbbVie, for providing statistical analysis support during the development of this manuscript. Medical writing support was provided by Stephanie J. Grice, MSc, and Paul MacCallum, PhD, of the Fishawack Communications Ltd.; funded by AbbVie.

References

- AASLD/IDSA American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) (2018). *HCV guidance: Recommendations for testing, managing, and treating hepatitis C*. Available at: . (Accessed 05 June 2018) <http://www.hcvguidelines.org>.
- Alavi, M., Grebely, J., Micallef, M., Dunlop, A. J., Balcomb, A. C., Day, C. A., et al. (2013). Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. *Clinical Infectious Diseases*, 57(Suppl. 2), S62–S69. <https://doi.org/10.1093/cid/cit305>.
- Asher, A. K., Portillo, C. J., Cooper, B. A., Dawson-Rose, C., Vlahov, D., & Page, K. A. (2016). Clinicians' views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs. *Substance Use and Misuse*, 51(9), 1218–1223. <https://doi.org/10.3109/10826084.2016.1161054>.
- Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., Dore, G. J., et al. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases*, 57(Suppl. 2), S80–S89. <https://doi.org/10.1093/cid/cit306>.
- Asselah, T., Kowdley, K. V., Zadeikis, N., Wang, S., Hassanein, T., Horsmans, Y., et al. (2017). Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. *Clinical Gastroenterology and Hepatology*, 16(3), 417–426. <https://doi.org/10.1016/j.cgh.2017.09.027>.
- Barua, S., Greenwald, R., Grebely, J., Dore, G. J., Swan, T., & Taylor, L. E. (2015). Restrictions for medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. *Annals of Internal Medicine*, 163(3), 215–223. <https://doi.org/10.7326/m15-0406>.
- Butner, J. L., Gupta, N., Fabian, C., Henry, S., Shi, J. M., & Tetrault, J. M. (2017). Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. *Journal of Substance Abuse Treatment*, 75(April), 49–53. <https://doi.org/10.1016/j.jsat.2016.12.014>.
- Chirikov, V. V., Marx, S. E., Manthana, S. R., Strezewski, J. P., & Saab, S. (2018). Development of a comprehensive dataset of hepatitis C patients and examination of disease epidemiology in the United States, 2013–2016. *Advances in Therapy*, 35(7), 1087–1102. <https://doi.org/10.1007/s12325-018-0721-1>.
- Christensen, S., Buggisch, P., Mauss, S., Boker, K. H. W., Schott, E., Klinker, H., et al. (2018). Direct-acting antiviral treatment of chronic HCV-infected patients on opioid substitution therapy: Still a concern in clinical practice? *Addiction*, 113(5), 868–882. <https://doi.org/10.1111/add.14128>.
- Cunningham, E. B., Applegate, T. L., Lloyd, A. R., Dore, G. J., & Grebely, J. (2015). Mixed HCV infection and reinfection in people who inject drugs—Impact on therapy. *Nature Reviews: Gastroenterology & Hepatology*, 12(4), 218–230. <https://doi.org/10.1038/nrgastro.2015.36>.
- Degenhardt, L., Peacock, A., Colledge, S., Leung, J., Grebely, J., Vickerman, P., et al. (2017). Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: A multistage systematic review. *Lancet Global Health*, 5(12), e1192–e1207. [https://doi.org/10.1016/S2214-109X\(17\)30375-3](https://doi.org/10.1016/S2214-109X(17)30375-3).
- Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., et al. (2016). Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: A randomized trial. *Annals of Internal Medicine*, 165(9), 625–634. <https://doi.org/10.7326/m16-0816>.
- EASL (2018). EASL recommendations on treatment of hepatitis C 2018. *Journal of Hepatology*, 69(2), 461–511. <https://doi.org/10.1016/j.jhep.2018.03.026>.
- Forns, X., Lee, S. S., Valdes, J., Lens, S., Ghalib, R., Aguilar, H., et al. (2017). Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): A single-arm, open-label, multicentre phase 3 trial. *Lancet Infectious Diseases*, 17(10), 1062–1068. [https://doi.org/10.1016/S1473-3099\(17\)30496-6](https://doi.org/10.1016/S1473-3099(17)30496-6).

- Gane, E., Poordad, F., Wang, S., Asatryan, A., Kwo, P. Y., Lalezari, J., et al. (2016). High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. *Gastroenterology*, 151(4), <https://doi.org/10.1053/j.gastro.2016.07.020> 651–659.e1.
- Gane, E., Lawitz, E., Pugatch, D., Papatheodoridis, G., Brau, N., Brown, A., et al. (2017). Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *New England Journal of Medicine*, 377(15), 1448–1455. <https://doi.org/10.1056/NEJMoa1704053>.
- Gidding, H. F., Law, M. G., Amin, J., Macdonald, G. A., Sasadeusz, J. J., Jones, T. L., et al. (2011). Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Medical Journal of Australia*, 194(8), 398–402.
- Grebely, J., Robaey, G., Bruggmann, P., Aghemo, A., Backmund, M., Bruneau, J., et al. (2015). Recommendations for the management of hepatitis C virus infection among people who inject drugs. *International Journal on Drug Policy*, 26(10), 1028–1038. <https://doi.org/10.1016/j.drugpo.2015.07.005>.
- Grebely, J., Mauss, S., Brown, A., Bronowicki, J. P., Puoti, M., Wyles, D., et al. (2016). Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of phase 3 ION trials. *Clinical Infectious Diseases*, 63(11), 1405–1411. <https://doi.org/10.1093/cid/ciw580>.
- Grebely, J., Bruneau, J., Lazarus, J. V., Dalgard, O., Bruggmann, P., Treloar, C., et al. (2017). Research priorities to achieve universal access to hepatitis C prevention, management and direct-acting antiviral treatment among people who inject drugs. *International Journal on Drug Policy*, 47(September), 51–60. <https://doi.org/10.1016/j.drugpo.2017.05.019>.
- Grebely, J., Dalgard, O., Conway, B., Cunningham, E. B., Bruggmann, P., Hajarizadeh, B., et al. (2018). Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): An open-label, single-arm, phase 4, multicentre trial. *The Lancet Gastroenterology & Hepatology*, 3(3), 153–161. [https://doi.org/10.1016/S2468-1253\(17\)30404-1](https://doi.org/10.1016/S2468-1253(17)30404-1).
- Grebely, J., Puoti, M., Wedemeyer, H., Cooper, C., Sulkowski, M. S., Foster, G. R., et al. (2018). Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin in patients with chronic hepatitis C virus genotype 1 infection receiving opioid substitution therapy: A post hoc analysis of 12 clinical trials. *Open Forum Infectious Diseases*, 5(11), <https://doi.org/10.1093/ofid/ofy248> ofy248.
- Hajarizadeh, B., Grebely, J., & Dore, G. J. (2013). Epidemiology and natural history of HCV infection. *Nature Reviews: Gastroenterology & Hepatology*, 10(9), 553–562. <https://doi.org/10.1038/nrgastro.2013.107>.
- Hajarizadeh, B., Cunningham, E. B., Reid, H., Law, M., Dore, G. J., & Grebely, J. (2018). Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: A systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*, 3(11), 754–767. [https://doi.org/10.1016/S2468-1253\(18\)30304-2](https://doi.org/10.1016/S2468-1253(18)30304-2).
- Harris, M., & Rhodes, T. (2013). Hepatitis C treatment access and uptake for people who inject drugs: A review mapping the role of social factors. *Harm Reduction Journal*, 10(May), 7. <https://doi.org/10.1186/1477-7517-10-7>.
- Kosloski, M. P., Zhao, W., Asatryan, A., Kort, J., Geoffroy, P., & Liu, W. (2017). No clinically relevant drug-drug interactions between methadone or buprenorphine-naloxone and antiviral combination glecaprevir and pibrentasvir. *Antimicrobial Agents and Chemotherapy*, 61(10), <https://doi.org/10.1128/aac.00958-17> e00958–17.
- Lalezari, J., Sullivan, J. G., Varunok, P., Galen, E., Kowdley, K. V., Rustgi, V., et al. (2015). Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. *Journal of Hepatology*, 63(2), 364–369. <https://doi.org/10.1016/j.jhep.2015.03.029>.
- Marshall, A. D., Cunningham, E. B., Nielsen, S., Aghemo, A., Alho, H., Backmund, M., et al. (2018). Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. *Lancet Gastroenterology & Hepatology*, 3(2), 125–133. [https://doi.org/10.1016/S2468-1253\(17\)30284-4](https://doi.org/10.1016/S2468-1253(17)30284-4).
- Mason, K., Dodd, Z., Guyton, M., Tookey, P., Lettner, B., Matelski, J., et al. (2017). Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada. *International Journal on Drug Policy*, 47(September), 202–208. <https://doi.org/10.1016/j.drugpo.2017.05.025>.
- Mavyret (2017). AbbVie, Inc. MAVYRET (glecaprevir and pibrentasvir) US prescribing information. Available at: . (Accessed: 05 June 2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209394s000lbl.pdf.
- Midgard, H., Bjoro, B., Maeland, A., Konopski, Z., Kileng, H., Damas, J. K., et al. (2016). Hepatitis C reinfection after sustained virological response. *Journal of Hepatology*, 64(5), 1020–1026. <https://doi.org/10.1016/j.jhep.2016.01.001>.
- Morris, L., Smirnov, A., Kvassay, A., Leslie, E., Kavanagh, R., Alexander, N., et al. (2017). Initial outcomes of integrated community-based hepatitis C treatment for people who inject drugs: Findings from the Queensland Injectors' Health Network. *International Journal on Drug Policy*, 47(September), 216–220. <https://doi.org/10.1016/j.drugpo.2017.05.056>.
- Ooka, K., Connolly, J. J., & Lim, J. K. (2017). Medicaid reimbursement for oral direct antiviral agents for the treatment of chronic hepatitis C. *American Journal of Gastroenterology*, 112(6), 828–832. <https://doi.org/10.1038/ajg.2017.87>.
- Read, P., Lothian, R., Chronister, K., Gilliver, R., Kearley, J., Dore, G. J., et al. (2017). Delivering direct acting antiviral therapy for hepatitis C to highly marginalised and current drug injecting populations in a targeted primary health care setting. *International Journal on Drug Policy*, 47(September), 209–215. <https://doi.org/10.1016/j.drugpo.2017.05.032>.
- Robaey, G., Bielen, R., Azar, D. G., Razavi, H., & Nevens, F. (2016). Global genotype distribution of hepatitis C viral infection among people who inject drugs. *Journal of Hepatology*, 65(6), 1094–1103. <https://doi.org/10.1016/j.jhep.2016.07.042>.
- Simmons, B., Saleem, J., Hill, A., Riley, R. D., & Cooke, G. S. (2016). Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: A systematic review and meta-analysis. *Clinical Infectious Diseases*, 62(6), 683–694. <https://doi.org/10.1093/cid/civ948>.
- WHO World Health Organization (2016). *Guidelines for the screening care and treatment of persons with chronic hepatitis C infection – Updated version April 2016*. Available at: . (Accessed 05 June 2018) <http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/>.
- Wolfe, D., Luhmann, N., Harris, M., Momenghalibaf, A., Albers, E., Byrne, J., et al. (2015). Human rights and access to hepatitis C treatment for people who inject drugs. *International Journal on Drug Policy*, 26(11), 1072–1080. <https://doi.org/10.1016/j.drugpo.2015.05.007>.
- Zeuzem, S., Foster, G. R., Wang, S., Asatryan, A., Gane, E., Feld, J. J., et al. (2018). Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. *New England Journal of Medicine*, 378(4), 354–369. <https://doi.org/10.1056/NEJMoa1702417>.